Clinical Implications

- A novel pathomechanism is proposed for the attenuated sweating found in patients with atopic dermatitis (AD).
- Sweating can be inhibited via H1-receptor activation.
- The use of H1 blockers is a novel approach to treating some patients with AD.

work of Matsui *et al.* (2014) now allows a rather compelling picture to fall into place.

The learning points

For clinicians, this paper shows that H1 blockers may be useful in AD, but only as an ''add on'', with close monitoring of responses. The second-generation antihistamines would be more useful than first-generation antihistamines, which are associated with a number of undesired effects, most importantly changes in REM sleep patterns and reduced cognitive function (Church *et al.*, 2010).

This paper also shows that we need better clinical trials in diseases such as AD, which have heterogeneous population bases. Individual treatment responses may be quite important. For investigators, the message is simple: apparently simple minor features of a disease may lead to novel findings; congratulations go to Matsui *et al.* (2014).

CONFLICT OF INTEREST
The authors state no conflict of interest.

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Alternative Models of Comorbidity: A Framework for the Interpretation of Epidemiological Association Studies

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Relationships between chronic diseases have emerged as major clinical, public health and research issues. Consequently, clinical and epidemiological research on comorbidities of skin diseases is increasingly recognized as an important tool to understand their etiologies more fully and to capture their morbidities and burdens. In this issue, Flohr and colleagues report a cross-sectional analysis on the complex associations among atopic dermatitis, filaggrin loss-of-function mutations, skin barrier function, and food sensitization in exclusively breastfed infants. When interpreting this and other association studies, various alternative models of comorbidity should be considered as suggested by Neale and Kendler.

Journal of Investigative Dermatology (2014) **134,** 303–307. doi:10.1038/jid.2013.527

Comorbidity studies in dermatology

With increasing life expectancy, the simultaneous presence of multiple pathological conditions in the form of comorbidity and multimorbidity has become common. The term ''comorbidity'' was coined initially to describe the occurrence of an independent medical condition in addition to an index disease (Feinstein, 1970). In a broader understanding, the term has been used interchangeably with ''multimorbidity'' to

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Clinical Implications

- Associations among atopic dermatitis (AD), filaggrin loss-of-function(FLG) mutations, skin barrier function, and food sensitivities do not yet provide a compelling, unified model for atopic disease.
- The study by Flohr *et al.* (2014) suggests that a defective skin barrier is related to both AD and food sensitization, but that this effect is independent from FLG genotype. Thus, stabilization of skin barrier function, e.g., through early emollient use, might prevent both traits independently from the individual molecular makeup, supporting the need for fresh prevention trials aimed at skin barrier enhancement.

describe the concurrent presence of two or more medically diagnosed diseases or even subclinical outcomes, whether causally related or not (Fried *et al.*, 2014).

AD is a common chronic relapsing inflammatory skin disorder that affects up to 20% of children and 3–5% of adults. Intractable itching associated with poor sleep and visible physical stigmata can lead to substantial problems in everyday life for affected patients and their families (Williams, 2005). Based on the frequent co-occurrence of atopic diseases and the established association of early AD with later asthma and rhinitis, the concept of the ''atopic march'' has been developed. Sensu stricto, the ''march'' implies a longitudinal progression of individuals through a predictable and sequential/overlapping series of phenotypes, from AD, food allergy, through asthma, and subsequently allergic rhinitis. However, this concept has been challenged by cohort studies (Flohr *et al.*, 2004; Williams and Flohr, 2006), and the postulated temporal and causal relationship between early AD and subsequent asthma deserves further investigation.

Recently, the association of AD with cancer (Wang and Diepgen, 2006), with other inflammatory disorders (Deckert *et al.*, 2013), and with mental disorders (Schmitt *et al.*, 2009; Romanos *et al.*, 2011) has gained increasing interest. In this issue, Flohr *et al.* (2014) report a cross-sectional analysis on the complex association between AD, FLG mutations, skin barrier function, and food sensitization (FS) in exclusively breastfed infants. We will discuss the implications of this study in more detail below.

Comorbidity is not only a hot topic in AD, but also in other important areas of dermatological research. The relationships between psoriasis and cardiovascular risk factors and cardiovascular disease on one hand and with psychiatric disorders on the other hand are under intensive investigation (Nijsten and Wakkee, 2009).

Two major objectives appear to stimulate comorbidity studies:

1. To investigate the etiology of disease. Understanding the underlying biological mechanisms of co-occurrence of diseases offers a key to understanding disease pathobiology. Eventually, this may lead to preventive or curative interventions.
2. To capture the whole spectrum of morbidity and burden of disease. This is important, not only from the public health perspective, but also for individualized, patient-oriented, interdisciplinary methods of care.

These objectives identify co-occurrence of disorders as an important area for experimental, clinical, epidemiological, and methodological investigation, and they explain why comorbidity studies have gained interest in dermatological research.

However, the interpretations of comorbidity studies are not straight forward, as different models of disease associations, as well as sources of bias must be considered. Neale and Kendler (1995) provided a comprehensive set of possible comorbidity models that offer a framework for the interpretation of epidemiological association studies. We believe that this framework may be of considerable value for interpreting comorbidity studies in dermatology. Before introducing this framework, we will summarize the main findings by Flohr *et al.* (2014) in this issue and then apply the framework to their study.

Key study characteristics and findings from Flohr *et al.*

The study included 619 exclusively breastfed infants (age 3 months), that were recruited from the general population by advertisements for an interventional trial to prevent food allergy. Children were examined for AD, disease severity was determined by means of the Scoring Atopic Dermatitis (SCORAD) index, transepidermal water loss (TEWL) was measured as an indicator of skin barrier function, the six most common FLG mutations were genotyped, and skin prick testing was performed for six common allergenic foods. Approximately 25% of the children (154/619) were diagnosed as having AD, most of whom (86%; $n=132$) were classified as having mild AD (SCORAD <20). Twelve percent of the children ($n=75$) carried at least one FLG mutation, 5.5% ($n=34$) were sensitive to at least one of the six study foods. As expected, AD was associated with higher prevalence of FLG mutations (37/154 children with AD; 24%) and with higher median TEWL, indicating impaired skin barrier function. AD was associated with FS, with moderate-to-severe AD being associated with FS more strongly than mild AD. However, the reported association between AD severity and FS was based on low numbers (nine comorbid participants with moderate-to-severe AD). FLG mutations were not significantly related to FS (odds ratio 1.21). TEWL was associated with FS and remained an independent determinant, after adjusting for AD presence and FLG mutation status.

Framework for interpreting comorbidity studies

The underlying assumption of the Neale and Kendler (1995) models is that there is a continuous liability distribution of multifactorial causes for a disorder. The disorder manifests in an individual if a defined threshold in that liability distribution is reached. This so-called

Table 1. Description of the Neale and Kendler (1995) models of comorbidity and application to the study by Flohr *et al.* (2014) on the association between atopic dermatitis (AD) and food sensitization (FS)

Name of model	Description	Application to findings by Flohr *et al.* (2004) on the comorbidity between AD and FS
Artificial sources of comorbidity		
Chance	Comorbidity is due to chance.	There was significantly greater comorbidity between AD and FS than would be expected by chance ($P \leqslant 0.001$). → *Model rejected.*
Sampling bias	Comorbid individuals are more likely to participate in study than individuals with only one single disease. Clinical samples and hospital studies are prone to sampling bias.	Participants were recruited from the general population through advertising for an interventional trial for food allergy prevention. → *Children at increased risk for food allergy and atopic disorders may be overrepresented. This possible bias unlikely explains the observed comorbidity.* → *Model rejected.*
Population stratification	If two disorders have non-overlapping sets of risk factors, but these risk factors both are more common in certain strata of the population, then significant comorbidity may be observed. Twin studies are prone to population stratification.	This was not a twin study. Participants were recruited from the general population. → *Model rejected.*
Non-causal models[a]		
Alternate forms	Comorbid conditions are different (alternate) manifestations of the same disorder. This model implies that comorbid cases are no different in mean liability than those who have only one of the disorders.	AD and food sensitization/food allergy differ in the immunological mechanisms and other major aspects of patho-etiology. Flohr *et al.* (2004) found FLG mutations to be associated with AD, but not with FS. → *Model rejected.*
Random multiformity	Excess comorbidity occurs because some cases of one disorder are epiphenomena (phenocopies) of the second disorder, and/or vice versa, although both disorders have unrelated liabilities.	It has been observed previously (Flohr *et al.*, 2004) that those with more severe AD are also more likely to be sensitized. It has been speculated, that atopy (allergic sensitization) might be an easily measurable epiphenomena of AD that does not necessarily have an important causative role (Williams and Flohr, 2006). The findings by Flohr *et al.* (2014) allow the interpretation that FS is an epiphenomenon of more severe AD without related liabilities between both disorders. → *Model not rejected.*
Extreme multiformity	Similar to random multiformity, but phenocopies of the second disorder arise only at the extreme of the distribution of liability of the other disorder, i.e., the most severely affected persons.	Flohr *et al.* (2014) report that the prevalence of FS is also increased in children with mild AD. →*Model rejected.* (Assuming the SCORAD is an adequate instrument to capture the liability distribution of AD)
Three independent disorders	Two disorders are entirely independent. The comorbid disorder is a third independent dimension, unrelated to either disorder occurring alone.	The study by Flohr *et al.* (2014) does neither confirm nor reject the hypothesis that *AD plus (with) FS* constitutes a distinct entity or a syndrome. → *Model not rejected.*
Causal models		
Correlated liabilities/risk factors	Both conditions share genetic and/or environmental risk factors. Common underlying risk factors explain excess comorbidity.	Flohr *et al.* (2014) found FLG mutations to be associated with AD, but not with FS. Other genetic analyses that may confirm correlated underlying susceptibility for AD and FS have not been reported. AD and FS might share environmental risk factors (e.g., those involved in the hygiene hypothesis), but this was beyond the scope of the study by Flohr *et al.* (2014). In addition to not yet identified genetic factors, factors of the physical environment might be a possible common risk factor for both AD and FS given that Flohr *et al.* (2004) found an association between TEWL and FS when adjusting for AD. → *Model not rejected.*
Reciprocal causation	Both disorders cause each other.	Cross-sectional studies are unsuitable to study causation. Therefore, the study presented by Flohr *et al.* (2014) can neither confirm nor reject the hypothesis that AD causes FS or vice versa. Based on our current understanding of the pathophysiology of FS, AD does not qualify as a potential cause. → *Reciprocal causation rejected.*

Table 1 Continued on following page

Table 1. (Continued)

Name of model	Description	Application to findings by Flohr *et al.* (2004) on the comorbidity between AD and FS
Causal model	One disorder is risk factor for the other.	It is known that food allergy can trigger AD and induce exacerbation. Therefore, it is possible that all or some of the nine children with more severe AD (SCORAD >20) and FS in the sample of Flohr *et al.* (2014) actually have food allergy-triggered AD. If we consider trigger factors as causes of AD, then FS might be a cause of at least a subgroup of children with AD. → *Causal model not rejected.*

[a]Ordered from the closest to the most distant relationship.

''continuous liability threshold'' model applies to AD, food allergy, and other multifactorial disorders. Neale and Kendler (1995) specified different alternative comorbidity models: Three models describe artificial sources of comorbidity, four ''true'' but non-causal models of comorbidity (i.e., alternate forms, different multiformity models, three independent disorders model), and three causal models of comorbidity (i.e., correlated liabilities, causal model, and reciprocal causation).

Table 1 provides a description of the comorbidity models and several arguments about whether models are in accordance with the findings of Flohr *et al.* (2014).

Potential models for an association between AD and allergic sensitization to foods

Based on the report by Flohr *et al.* (2014), all three models describing artificial sources of comorbidity can be rejected. Children at increased risk for food allergy and atopic disorders may be overrepresented, but this potential source of sampling bias cannot fully explain the observed comorbidity between AD and FS. The observation that FLG mutations were associated with AD, but not with FS, leads to the rejection of the alternate forms model, i.e., that AD and FS are alternate manifestations of one underlying disorder.

One possible model that explains the observed comorbidity between AD and FS is random multiformity. This term means that excess comorbidity occurs because some cases of one disorder are epiphenomena (phenocopies) of the second disorder, although both disorders have unrelated liabilities. It has been speculated previously that atopy (allergic sensitization) is an ''easy to measure'' epiphenomenon of AD, one that does not necessarily have a causative role (Flohr *et al.*, 2004; Williams and Flohr, 2006). The findings of the present study (Flohr *et al.*, 2014) do not exclude the hypothesis that FS is an epiphenomenon of more severe AD without related liabilities between both disorders. The three independent disorders model, i.e., that the comorbid state ''AD plus FS'' constitutes a distinct entity or a syndrome as it has also been suggested for the complex endophenotype AD + asthma in the context of FLG studies (Rodriguez *et al.*, 2009) cannot be excluded, based on the presented study.

Although cross-sectional analyses are generally not suitable to draw conclusions about causality, the findings by Flohr *et al.* (2014) offer several useful findings for speculations about the three different causal models of comorbidity as introduced by Neale and Kendler (1995). As discussed by the authors, the correlated liabilities/risk factors model, i.e., that AD and FS share genetic and/or environmental risk factors, offers one possible interpretation of the study findings. In addition to yet unknown genetic factors, factors of the physical environment and/or factors involved in the hygiene hypothesis might be common risk factors for both AD and FS given that Flohr *et al.* (2014) observed a significant association between TEWL and FS when adjusting for AD. Alternatively, the causal model might apply. It is well known that food allergy may, especially in small children, trigger AD flares. Therefore, it is possible that all or some of the nine children with more severe AD (SCORAD >20) and FS in the sample of Flohr *et al.* (2014) actually have food allergies that trigger AD. If we consider trigger factors as causes of AD, then FS might be a cause of AD. For more details on the models of comorbidity and their application to the study by Flohr *et al.* (2014), please refer to Table 1.

Questions for future research

Research is necessary to identify the most appropriate model of comorbidity between AD and FS. Follow-up of the cohort of exclusively breastfed children and results of the embedded prevention trial (Flohr *et al.*, 2014) are expected to add significantly to our understanding of the mechanisms underlying the observed co-occurrence between AD and FS. Molecular research is necessary to determine whether AD and FS share underlying risk factors, e.g., intermediate molecular mechanisms of inflammation (''subclinical traits'') of relevance across traditional diseases entities, what proportion of excess comorbidity is caused by FS-triggered (caused) AD, and whether FS is (only) an epiphenomenon of AD. Only with this information can the most appropriate model of comorbidity-targeted prevention and care strategies be developed.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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IL-17: A Key Player in the *P. acnes* Inflammatory Cascade?

Diane M. Thiboutot[1], Alison M. Layton[2] and E. Anne Eady[2]

Recent advances in our understanding of inflammatory skin diseases now afford an opportunity to delve deeper into microbial/host interactions in acne. Agak *et al.* report that *Propionibacterium acnes* induces IL-17 expression in peripheral blood mononuclear cells and present new evidence that IL-17 + cells are found in the perifollicular infiltrate of comedones. Additional studies are needed to assess the clinical relevance of IL-17 in acne.

Journal of Investigative Dermatology (2014) **134,** 307–310. doi:10.1038/jid.2013.400

Plewig and Kligman (2000) wrote that ''Sebum is the fuel of the acne flame''. The question is ''How did the fire get started?''.

In this issue, Agak *et al.* (2014) present a series of experiments that support a role for IL-17 in the pathogenesis of acne. They demonstrate that *Propionibacterium acnes* induces IL-17 expression in human peripheral blood mononuclear cells (PBMCs) from healthy individuals *in vitro* and that supernatants from cultures of *P. acnes* incubated with PBMCs induce naive CD4 + CD45TA + T cells to differentiate into Th17 cells (expressing Th17, RORα, and RORc) and Th1 cells (expressing IFNγ). By using a panel of neutralizing antibodies, they determined that IL-1β, IL-6, and transforming growth factor-β (TGFβ) regulate *P. acnes*–induced IL-17 responses as they do in other systems. Furthermore, the authors suggest that the clinical relevance for these findings is supported by the identification of IL-17 + cells in perifollicular infiltrates in biopsies of typical closed comedone-type acne lesions. Before concluding that these findings are relevant in the pathogenesis of acne, links need to be made between the *in vitro* and *in vivo* data. For example, is *P. acnes* present universally in follicles surrounded by an infiltrate containing IL-17-positive cells and what type of cells are they? In addition to providing potential insight into acne pathogenesis, these data raise questions regarding the multiplicity of mechanisms by which *P. acnes* interacts with immune cells *in vivo*, the sequence of events that initiates and terminates inflammatory responses in acne and the possible role of IL-17. Furthermore, demonstration of the ability of all *trans* retinoic acid (ATRA) and vitamin D to suppress *P. acnes*–induced generation of Th17 cells suggests a potential new mechanism of action whereby retinoids and vitamin D might modulate acne inflammation physiologically or even pharmacologically.

How does *P. acnes* wage war in acne?

P. acnes is a commensal organism that colonizes the pilosebaceous follicles of people with and without acne. Although not a classical pathogen, *P. acnes* have the capacity to contribute to the genesis of inflammatory acne via multiple pathways (Table 1). Several *in vitro* studies demonstrate that *P. acnes* whole cells or cell fractions stimulate cytokine and matrix metalloproteinase release from immune cells, keratinocytes, and sebocytes (Kim *et al.*, 2002; Liu *et al.*, 2005; Nagy *et al.*, 2006; Lee *et al.*, 2010) (Figure 1a and b).

The mechanism by which *P. acnes* exerts its effects on these cells *in vivo* is unknown, perhaps via direct contact, secreted factors, or secondary events (Table 1). *P. acnes* resides mainly in the microaerophilc deeper portions of healthy follicles where it comes in contact with follicular keratinocytes and cells within the proximal region of the sebaceous duct. Within comedones, it multiplies within the sebum-filled lacunae that form inside of the cornified plugs. It can be envisioned that *P. acnes* whole cells, cell fragments, and/or secreted factors may exert proinflammatory effects on follicular keratinocytes. *P. acnes* comes in direct contact with the cells within the dermis following follicular rupture, a late finding in the development of inflammatory acne lesions (Plewig and Kligman, 2000). Soluble factors, however, may escape

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